***S*topping *P*erioperative *A*ngiotensin II *C*onverting *E*nzyme inhibitors and/or receptor blockers in major non-cardiac surgery (SPACE): a phase II, explanatory, randomised controlled trial.**

Short title:	SPACE trial
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REC reference:	16/LO/1495
EudraCT reference:	2016-004141-90

SIGNATURE PAGE

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol (version 8.0, 28/01/2022) or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Policy Framework for Health & Social Care research (2017), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Statistician Agreement Page

The clinical study as detailed within this research protocol (version 8.0, 28/01/2022), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Policy Framework for Health & Social Care research (2017), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Principal Investigator Agreement Page

The clinical study, as detailed within this research protocol (version 8.0, 28/01/2022), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Policy Framework for Health & Social Care research (2017), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

SUMMARY

TITLE	*S*topping *P*erioperative *A*ngiotensin II *C*onverting *E*nzyme inhibitors and/or angiotensin-II receptor blockers in major non-cardiac surgery (SPACE): a phase II, explanatory, randomised controlled trial.
SHORT TITLE	SPACE
Protocol Version & Date	Version 8.0 28/01/2022
Methodology	Randomised controlled interventional trial.
Study Duration	65 months
Study Centres	Barts Health NHS Trust, University College London Hospitals NHS Foundation Trust, County Durham & Darlington NHS Foundation Trust, Plymouth Hospitals NHS Trust, University Hospitals Bristol NHS Foundation Trust
Objectives	To determine whether continuing angiotensin-II converting-enzyme inhibitors (ACE-I) and/or angiotensin-II receptor blockers (ARB) reduces the risk of myocardial injury, identified using high-sensitivity plasma troponin measurement during the first 48 hours after surgery.
Phase of the Trial	Phase II
Number of Patients	260 patients (130 per arm)
Main Inclusion Criteria	Patients aged 60 years and over receiving chronic angiotensin II converting enzyme inhibitors and/or receptor blockers and undergoing major surgery requiring general and/or regional anaesthesia with sedation.
Statistical Analysis	The analysis will be conducted on an intention-to-treat basis; all participants with a recorded outcome will be analysed according to the treatment group to which they were randomised.

GLOSSARY OF TERMS AND ABBREVIATIONS

ACE-I	Angiotensin-Converting-Enzyme Inhibitor
AE	Adverse Event
AR	Adverse Reaction
ARB	Angiotensin-II Receptor Blocker
BP	Blood Pressure
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
ECG	Electrocardiograms
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Patient Information Sheet
PSF	Pharmacy Site File
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SSI	Surgical Site Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

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1 INTRODUCTION

1.1 Background

A triad of myocardial injury,[1] immunosuppression[2, 3] and persistent autonomic dysfunction[4, 5] is observed in high-risk patients following major surgery, leading to infection, organ failure, delayed recovery and/or death. Prolonged activation of neurohormones such as angiotensin-II correlates with tissue injury.[6, 7] Around 40% of surgical patients most at risk of postoperative complications are prescribed angiotensin-II converting enzyme inhibitors (ACE-I) or angiotensin-II receptor blockers (ARB).[8] These drugs are first-line therapy for improving outcomes from several chronic diseases, including hypertension, chronic kidney disease and cardiac failure. The use of ACE-I and/or ARB is set to rise dramatically, with the recent publication of the landmark SPRINT trial, which shows that lowering blood pressure (BP) control targets to systolic ≤120mmHg reduces mortality.[9] ACE-I and/or ARB are frequently stopped before surgery in the widely held belief that this prevents intraoperative hypotension, although robust evidence for this is lacking.

1.2 Investigational medicinal product

ACE-I and/or ARB are orally administered drugs prescribed for hypertension, chronic kidney disease and cardiac failure. The choices of ACE-I and/or ARB drugs is already established by the responsible clinician and are not described within this protocol. The responsible clinician can use any other antihypertensive medication for optimal patient care in addition to the ACE-I and/or ARB to achieve target BP in those cases, which remain difficult to control, and if the clinician decides it is required. All investigational medicinal products (IMP) used in this study will be within its' UK licenced indication.

1.3 Preclinical data

ACE-I and/or ARB are established treatments for patients with hypertension, chronic kidney disease and cardiac failure. Drug metabolism, pharmacokinetics and toxicological data are well established for these indications; in the SPACE trial, these drugs will be continued or stopped as per normal clinical practice. The decision to restart ACE-I and/or ARB in SPACE will be confirmed by the Principal Investigator (PI) at each site. There may be a delay in restarting the drugs (for patients in whom they have been stopped preoperatively) on postoperative day 2, if BP is low and/or the presence of acute kidney injury, according to the protocol criteria.

1.4 Clinical data

UK practice and international guidelines reflect clinical uncertainty regarding ACE-I and/or ARB withdrawal.[1, 2] However, a strong association exists between stopping ACE-I and/or ARB and an increased risk of mortality.[3, 4] These epidemiologic data suggest that acute withdrawal of ACE-I and/or ARB, coupled with upregulation of the angiotensin receptor as a result of chronic ACE-I and/or ARB therapy and substantial elevations in angiotensin-2, could be directly injurious, leading to excess postoperative morbidity and mortality. This hypothesis is highly plausible since the use of ACE-I and/or ARB reduces cardiovascular morbidity,[5 6] and inflammation,[7] particularly in patients with established cardiovascular and chronic kidney disease.

1.5 Rationale and risks/ benefits

We do not currently know whether ACE-I and/or ARB should be stopped or continued in major surgery. Furthermore, our current mechanistic understanding suggests that ACE-I and/or ARB may confer organ protection in the perioperative period. There may be benefits of administering these drugs throughout the perioperative period, by counteracting the harmful effects of high levels of angiotensin-II following the stress of surgery. There may also be harm as a result of lowering BP, which can affect kidney function and the heart. There is an acceptable risk-benefit ratio, exemplified by the fact that some clinicians continue these drugs while others stop them prior to surgery in the absence of interventional trial data.

2 TRIAL OBJECTIVES AND DESIGN

2.1 Trial objectives

Primary objective – To determine whether continuing perioperative ACE-I and/or ARB reduces the risk of myocardial injury, identified using high-sensitivity plasma troponin measurement during the first 48 hours after surgery.

Secondary objective – To determine whether continuing perioperative ACE-I and/or ARB reduces the risk of postoperative morbidity.

Tertiary objective – To determine whether continuing perioperative ACE-I and/or ARB results in changes to perioperative heart rate, blood pressure or immune function.

Primary outcome measure

The primary outcome is myocardial injury, a binary variable based on plasma high sensitivity Troponin-T) measured in blood samples collected immediately before the induction of anaesthesia, and then postoperative day 1± 6 hours and day 2 ± 6 hours after surgery. The primary outcome is met under the following conditions:

1. Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L *OR*
2. Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L

Secondary outcome measures

1. Highest level of Troponin-T measured within 48 hours of surgery (continuous variable)
2. Infection within 30 days of surgery*
3. Myocardial infarction within 30 days of surgery*
4. Acute heart failure within 30 days of surgery*
5. Stroke within 30 days of surgery*

Tertiary outcome measures

Changes in heart rate, blood pressure and tests of immune function.

2.2 Safety outcomes

1. Hypotension from randomisation until 48 hours after surgery*
2. Hypertension from randomisation until 48 hours after surgery*
3. Arrhythmias from randomisation until 48 hours after surgery*
4. Acute Kidney Injury (KDIGO grades 1-3 within 30 days after surgery*

*defined according to clinical criteria, see appendix 2

2.3 Process measures

1. Duration of hospital stay after surgery
2. Unplanned critical care admission (level 2 and 3), including a planned critical care unit stay prolonged by a complication.

2.4 Assessment of primary and secondary outcomes

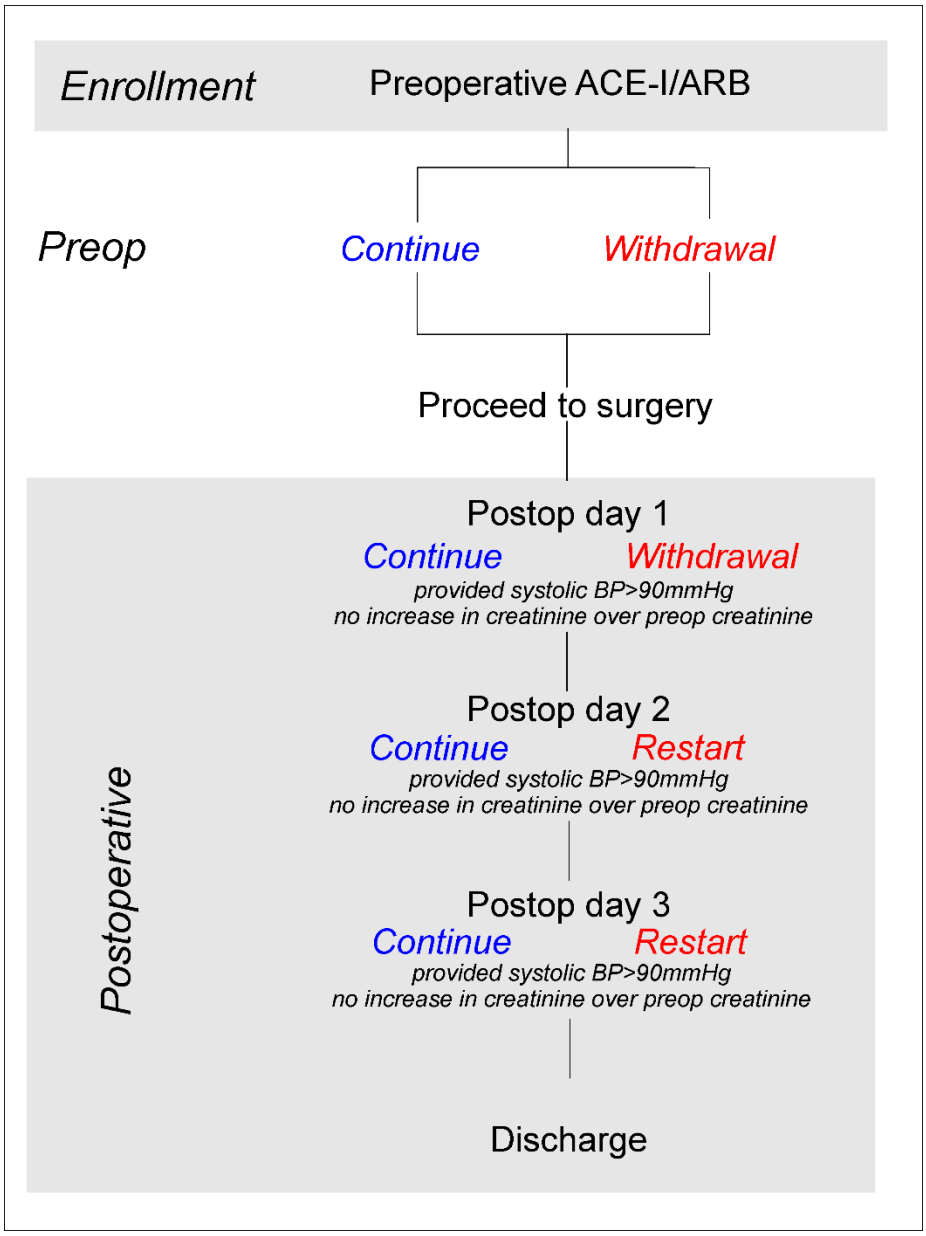
For the primary outcome, additional blood samples will be collected immediately on the day of surgery before the induction of anaesthesia, and then at 24 and 48 hours after surgery to measure the Troponin T levels. This will be typically collected by a research nurse. For the secondary outcome measures (postoperative complications of Clavien-Dindo grade II or higher within 30 days of surgery), an initial assessment will be made by a research associate or research nurse, but may include physicians and surgeons. The initial assessment will be based on clinical information from patients' medical record, including (but not limited to) clinical notes, microbiology test results, blood test results, drug prescription charts, radiology tests etc. Patients discharged from hospital before day 30 will be contacted shortly after day 30 to ascertain whether they have received any new treatment, been re-admitted to hospital or seen a doctor since hospital discharge. For patients who have received further treatment or seen a health professional since discharge, further details will be collected directly from the hospital/doctor or from the patient's medical record. The investigator making the initial assessment should not have been involved in the patient's care, and should be unaware of their treatment group allocation.

If the initial outcome assessment is 'no' for any of the secondary outcome measures, then the patient's outcome is classified as 'no postoperative complication'. Where a complication has been identified, then this should be verified by the site PI or suitably qualified delegate. This decision is final. The PI or designee should only undertake this evaluation if they are unaware of the patient's treatment group allocation. If they are aware of the treatment allocation, they should delegate this evaluation to a deputy who is unaware of treatment group allocation.

2.5 Trial design

Phase II, explanatory randomised trial, with open study group allocation and blinded primary outcome assessment.

2.6 Study scheme diagram



3 SUBJECT SELECTION

3.1 Number of subjects and subject selection

Target accrual for the study is 260 patients over 65 months. Patients aged 60 years and over, on chronic ACE-I and/or ARB therapy and undergoing major surgery (e.g. joint replacement, vascular, gastrointestinal surgery) lasting more than 120 minutes requiring general and/or regional anaesthesia with sedation. Patients will be selected for the study from preoperative assessment outpatient clinics and/or referring surgeons (no use of advertisements). Patients will be contacted during their preoperative hospital visit; vulnerable groups will not be included.

3.2 Inclusion criteria

- Informed consent (no incapacitated or vulnerable adult or minors will be included).
- Age 60 years and over.
- Undergoing major surgery (e.g. major joint replacement or vascular or gastrointestinal) requiring general and/or regional anaesthesia with sedation.
- Currently taking ACE-I, ARB or combined ACE-I and ARB therapy or combination therapy where medication includes ACE-I or ARB (e.g. thiazide diuretic and ACE-I).
- Expected duration of surgery longer than 120 minutes.
- American Society of Anesthesiologists physical status grade 3 or above.
- All female subjects must be postmenopausal, as demonstrated by clinical history, or demonstrated not to be pregnant though a preoperative pregnancy test.

3.3 Exclusion criteria

- Current participation in any other trials where care or treatment is being altered.
- Recent myocardial infarction (within 3 months).
- Any condition, which in the opinion of the treating clinician, would result in the patient being harmed by the cessation of the ACE-I and/or ARB therapy.

3.4 Criteria for premature withdrawal

Systematic non-compliance (i.e. not stopping ACE-I and/or ARB on randomisation to that arm, or failure to restart the drug) may result in withdrawal from the study. Once withdrawn no further data will be collected.

4 INVESTIGATIONAL MEDICINAL PRODUCT

4.1 List and definition of each IMP, including placebos

Any ACE-I and ARB licensed for use in the treatment of hypertension, heart failure, chronic kidney disease and/or diabetes mellitus within the UK. Patients will be taking their usual prescribed ACE-I and/or ARB therapy.

As detailed in the British National Formulary, the following ACE-I and ARB medications are currently available and will be discontinued in those participants randomised to the cessation arm of the SPACE trial.

Candesartan	Perindopril Erbumine
Lisinopril	Perindopril Arginine
Irbesartan	Quinapril
Enalapril Maleate	Trandolapril
Telmisartan	Imidapril Hydrochloride
Ramipril	
Eprosartan	
Captopril	
Losartan	
Cilazopril	
Olmesartan	
Fosinopril Sodium	
Valsartan	
Moexipril Hydrochloride	
Azilsartan	

Any new ACE-I or ARB licenced within the study treatment period will also be accepted.

4.2 Formulation of IMP

There will be no IMP to source or label in either arm. Participants are randomised to either continue or stop ACE-I and/or ARB preoperatively. Participating hospital pharmacies will be responsible for the continued supply of medication for participants in each arm throughout the trial as per routine local clinical practice. The medication will be from a commercial stock in standard packaging. As the medication is a continuation of the participant's standard treatment from the local pharmacy's own stock it will not be labelled as an IMP.

4.3 IMP supply

Regulation 46 of The Medicines for Human Use (Clinical Trial) Regulations 2004 allows for a particular situation where specific trial labelling is not required. This applies to trials of marketed products being (a) used within the terms of their marketing authorisation, (b)

dispensed to a subject in accordance with a prescription given by an authorised health care professional and (c) labelled in accordance with the regulations that apply to dispensed relevant medicinal products. IMP in the SPACE trial are marketed products being used within the terms of their marketing authorisation. They will be dispensed to the participant in accordance with a prescription given by an authorised health care professional (the participant's responsible clinician) and will be labelled in accordance with the regulations that apply to dispensed relevant medical products. The medication will be commercial stock in standard packaging. Therefore, specific trial labelling is not required. The IMP to be used in the SPACE trial can be labelled with a standard pharmacy dispensing label under the exemption described above and participants issued with trial information cards. This is clearly documented in the submission in support of the Clinical Trials Authorisation (CTA) application.

4.4 Prescription of IMP

There will be no prescription of IMP by the study team as participants will already be taking the IMP on admission to the study. The study team will only suspend the IMP the participant is usually taking when randomized to withdraw, according to the half-life of the drug, to ensure it has been stopped for an adequate period of time to allow "washout".

4.5 Preparation and administration of IMP

IMP in the SPACE trial are marketed products being used within the terms of their marketing authorisation. The medication will be commercial stock in standard packaging. Specific trial labelling is not required. No changes from local NHS trust standard procedure will occur.

4.6 Prior and concomitant therapies

All prior and concomitant treatments that the subjects take can continue whilst on treatment on the study (this may also include non-medicinal products). The case reporting forms (CRF) will capture data on any prior or concomitant therapies.

4.7 Dose modification/ reduction/ delay

Resumption or continuation of ACE-I and/or ARB in SPACE will not require dose modifications. There may be a delay in restarting the drugs (for patients in whom they have been stopped preoperatively) on postoperative day 2, if BP is low (<90mmHg) and/or the presence of acute kidney injury, according to the protocol criteria (please see study scheme

diagram section 2.6). The decision to restart ACE-I and/or ARB will be confirmed by the PI at each site.

4.8 Return/ recall or destruction of IMP

There will be no IMP returns or destructions as part of this study. Drug recall will be through the standard local NHS dispensing pharmacy recall process.

5 STUDY PROCEDURES

5.1 Screening procedures

Potential participants will be screened for eligibility by a member of the research team at the site, having been identified from pre-admission clinic lists, operating theatre lists or surgical wards in the case of patients admitted prior to surgery for other investigations. All patients that undergo screening will be recorded on the screening log. Before surgery, potential participants will be identified and approached by a member of the research team, who are considered part of the direct care team. Due to nature of the intervention patients will not be enrolled on the day of surgery.

5.2 Informed consent procedures

It is the responsibility of the PI or appropriately trained delegate (where possible a medically qualified person) to obtain consent. All staff taking consent will be trained in taking consent and this will be evidenced on the Delegation log, they will also have appropriate Good Clinical Practice (GCP) training. If for some reason an investigator is not available in person or by phone and the participant wishes to speak with them before providing consent, a second consent visit should be arranged. The consent process will include provision of a patient information sheet (PIS) accompanied by an informed consent form (ICF) and, an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. This will either take place face to face or via a locally approved electronic medium (phone, video conferencing etc.). All potential participants will be provided with a copy of the PIS and ICF either in person, via email or by post. If participants agree to take part they would be asked to sign and return the ICF via email or by post. The PI or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial for any reason. Patients who lack capacity to give or withhold informed consent will not be recruited. Patients who are not entered into this trial should be recorded (including reason not entered) on the screening log in the Investigator Site File.

As required by GCP, the patient should be given ample time to consider giving their consent for the trial. It is felt that 24 hours gives sufficient time for the patient to consider their participation within the study and give informed consent. If for any reason, less than 24 hours is to be given, this will be clearly documented in the medical notes along with justification for this decision. The date that the PIS is given to the patient must be documented within the patient's notes to ensure that sufficient time is given (minimum 24 hours).

If any further safety information arises, which may result in significant changes in the risk/benefit analysis, the PIS and ICF must be reviewed and if applicable updated accordingly.

5.3 Randomisation procedures

Once a medically qualified member of the research team has confirmed the patient's eligibility, the process of randomisation can commence. Randomisation will occur after the participant has provided informed consent, but 72 hours before the surgical procedure is due to start. Participants will be centrally allocated to a treatment group in a 1:1 ratio using a computer generated dynamic procedure (minimisation) with a random component.

Minimisation variables are trial centre, surgical procedure category (surgery involving the gut AND all other surgery) and ACE-I/ARB category (ACE-I or ARB). Each participant will be allocated with 80% probability to the treatment group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. The allocation sequence is generated by an automated algorithm and is concealed to all trial investigators. The system for generating the allocation sequence is bespoke and was developed in–house; it has been validated for use by the trial statistician, Tahania Ahmad, Queen Mary University of London.

To enter a patient into the SPACE trial, research staff at the site will log on to a secure web-based randomisation and data entry platform hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and treatment group allocation. Patients will receive a patient advice letter confirming their treatment group allocation. In addition, patients will be told in person or by telephone, together with a reminder(s) via text message before hospital admission. Research staff will document randomisation allocation on the CRF. Once the patient has been successfully allocated to a treatment group, this will be documented in the enrolment log.

5.4 Blinding and procedures to minimise bias

This is an open-label trial. Trial participants and staff will not be blinded to treatment group allocation. Local investigators responsible for randomisation and the intervention will not be blinded to treatment group allocation. Where possible, local investigators collecting follow-up data and investigators at the central coordinating centre will be blinded to treatment group allocation. The primary outcome measure (myocardial injury) will be blinded to all investigators until after the last participant has undergone surgery. Since this is an open-label trial, procedures for un-blinding are not required.

5.5 Schedule of treatment for each visit

The trial intervention period will commence 72 hours prior to day of surgery and continue for at least 48 hours after surgery. After randomisation, participants will receive a patient advice letter confirming their treatment group allocation, to stopping or continuing their ACE-I and/or ARB. Participants will also be reminded by telephone call and/or text message, or in person if they are in hospital. If the patients are not in hospital, they will receive a telephone call and/or text message or visit the day before surgery. ACE-I and/or ARB will be continued or discontinued as per treatment group allocation and this will continue until 48 hours after the end of surgery. Since ACE-I and ARB have differing durations of action, participants will receive drug-specific instructions as to when to stop. When the ACE-I and/or ARB duration of action is equal to, or more than, 24 hours, the drug will be stopped 48 hours prior to surgery. All other ACE-I and/or ARB will be stopped on the day before surgery (see appendix for specific drugs' half-life and duration of action).

5.6 Schedule of assessment in diagrammatic format

Event/Visit	Screening	Pre-op 72 hrs before surgery	Pre-op ≥ 48 hrs before surgery	Day of surgery	Postop day 1 ± 6 hrs	Postop day 2 ± 6 hrs	Postop day 3 ± 6 hrs (if subject was not discharged on postop day 2)	30 days after surgery
Inclusion/exclusion criteria	x							
Informed consent	x							
Demographic information	x							
Medical history	x							
Prior and concomitant medications	x			x	x	x	x	x
Height and weight				x				
EQ-5D-3L	x							x
Planned level of care	x							
Level of care				x	x	x	x	
Randomisation		x						
Perioperative information				x				
Review of medical notes	x		x		x	x	x	x
Restart drug						x		
Blood sample			x*	x	x	x		
Hemoglobin †	x†							
Creatinine †	x†			x	x	x	x	
Blood pressure/ heart rate[s]				x	x	x		
Intravenous fluids				x	x	x	x	x
Telephone contact			x					x
Review of AE/SAE				x	x	x	x	
End of trial form								x

* provided patient is in hospital.

† within 4 weeks prior to surgery

[S] At some centres heart rate may be measured with a Holter monitor and blood pressure cuff to collect ambulatory blood pressure (ABP) and in other sites the data will be obtained from the clinical notes. The Holter monitor and BP cuff will be loaned to the site by the Sponsor.

5.7 Follow-up procedures

Participants will be followed up on days 1, 2, and 3 (if the patient remains in hospital) after surgery. The end of the study is defined as the point when the last patient has completed 30-day follow-up. The follow-up will be completed over the telephone and therefore the paper CRF will be the source data for any patient-reported outcomes during this period. To minimise bias, follow-up data will be collected by a study team member who is blinded to the treatment group allocation. Similarly, investigators will review a participant's medical record (paper or

electronic) after surgery, unaware of the primary outcome result (which is measured after the end of the trial).

5.8 Laboratory assessments

Troponin-T (Elecsys, Roche Diagnostics) will be measured ≥ 48 hours before surgery (provided the patient is in hospital), on the day of surgery before induction of anesthesia and days 1 (± 6 hrs) and 2 (± 6 hrs) after surgery by The Doctors Laboratory, but the results will not be made available to the study team until the last study participant sample has been collected. Non-study clinicians and patients will remain blinded to the Troponin-T results throughout the study. Mechanistic studies for tertiary exploratory outcomes requiring assays of immune, neurohormonal function, electrocardiograms (ECG) and BP will be undertaken in laboratories based within Translational Medicine and Therapeutics, William Harvey Research Institute, Queen Mary University of London.

5.9 End of study definition

The end of the study is defined as the point when the last patient has completed their 30-day follow-up.

5.10 Procedures for un-blinding

Only the primary outcome of the study is blinded; therefore, treatment allocation is not blinded so no un-blinding procedures are required.

5.11 Subject withdrawal

All study participants are free to withdraw from the study at any time. All randomised patients will be included in the final analysis on an intention to treat basis, unless a participant specifically asks for their data not to be included.

5.12 Data collection and follow-up for withdrawn subjects

Patients that withdraw consent or drop out before randomisation will be replaced. The withdrawal will be documented in the CRF and medical records and although participants are not obliged to give the reason for withdrawing their consent, we will attempt to ascertain trends if possible relating to trial procedures, in case this results in a protocol amendment.

6 LABORATORIES

6.1 Central/ local laboratories

Troponin-T (Elecsys, Roche Diagnostics) will be measured from samples by The Doctors Laboratories (Whitfield Street, London, UK) at the end of the trial when all patient samples have been collected. Tertiary outcome measures and mechanistic studies requiring laboratory assays for immune, neurohormonal, ECG and BP function will be undertaken in laboratories based within Translational Medicine and Therapeutics, William Harvey Research Institute, Queen Mary University London. The blood samples taken at each time points will be centrifuged by the site and separated into four plasma and two serum cryotubes which will then be used for all required analyses.

6.2 Sample collection/ labelling/ logging

A blood sample of approximately 14ml should be collected into a serum separator tube and two EDTA tubes at each time point. All blood samples will be pseudo-anonymised. Samples collected at each NHS Site will be labelled with the corresponding SPACE trial ID and transferred to William Harvey Research Institute (WHRI). At the end of the study the samples will be transferred from WHRI to The Doctors Laboratory for analysis. All samples will be logged with regards to the date sent to the laboratory and the temperature/conditions at which it was sent to ensure the integrity and viability are not compromised. The full sample, collection, labelling, logging and transfer procedure will be documented in the study laboratory manual.

6.3 Sample receipt/ chain of custody/ accountability

Handling of the samples upon arrival at the laboratory will be documented. Upon receipt of the samples, the laboratory will ensure that the physical integrity of these samples have not been compromised in transit. If compromise has occurred, the study team, as well as the Sponsor, will be informed of this. Upon receipt of samples, laboratory staff will ensure that all samples are accounted for as per the labelling. All samples received will be logged in a sample log.

6.4 Sample analysis procedures

For high-sensitivity troponin analysis methodology, a standard measurement protocol will be undertaken.

6.5 Sample storage procedures

For the purposes of tertiary and exploratory outcome studies, leukocyte samples will be stored at -80ºC (unless they are tested immediately) in a dedicated research sample freezer based within Translational Medicine and Therapeutics, William Harvey Research Institute, John Vane Science Centre, Charterhouse Square, London, United Kingdom, EC1M 6BQ.

6.6 Data recording/ reporting

All troponin-T data will be measured by The Doctors Laboratory and shared by secure electronic communication after the last patient sample has been analysed.

7 PHARMACOVIGILANCE

7.1 General definitions

7.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an IMP, whether or not related to the IMP. Only cardiovascular events or events possibly related to the SPACE procedures will be recorded as AEs and assessed accordingly.

AEs that may be expected from acute perioperative discontinuation of ACE-I or ARB (or combination of both) are listed below. Cardiovascular events such as myocardial infarction (MI), stroke and heart failure could potentially be expected from ACE-I and/or ARB withdrawal but may equally be expected from undergoing major surgery in higher-risk patients who require ACE-I and/or ARB therapy. Note that each of these events are frequently observed in higher-risk surgical patients in normal practice, so also serve as secondary outcome measures for postoperative morbidity, as applicable:

1. Systolic BP>180mmHg from randomisation until 48 hours after surgery (as verified on measurement by study investigators)
2. Diastolic BP> 100mmHg from randomisation until 48 hours after surgery (as verified on measurement by study investigators)
3. Hypotension requiring pressor via central venous access from randomisation until 48 hours after surgery

4. Acute kidney injury, in the absence of haemorrhage/sepsis (KDIGO grades 1-4) within 30 days after surgery.

7.1.2 Adverse Reaction

An AR is any untoward and unintended response in a subject exposed to an IMP, which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as AR. The expression of a reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.1.3 Serious Adverse Event or Serious Adverse Reaction

Only cardiovascular events or events possibly related to the SPACE procedures will be assessed for seriousness and reported where appropriate.

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other important medical event

For the purposes of this study, it is up to the PI or a medically qualified delegate to decide whether the event caused the hospital stay to be prolonged. It is perfectly reasonable that patients have prolonged hospital stay due to other complications not related to the trial procedures.

A SAR is an AR that is classed as serious and which is consistent with the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC) for that product.

7.1.4 Suspected Unexpected Serious Adverse Reaction

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the reaction is not outlined in Section 4.8 of the SmPC for that product.

7.1.5 Event collection timing

AEs, SAEs and SUSARs will be collected from point of randomisation until post-operative day 3 only, as we would expect majority of the events to fall within this period.

7.2 Investigators assessment

7.2.1 Seriousness

The PI responsible for the care of the patient, or in his absence an authorised medically qualified person within the research team, and is responsible for assessing whether the event is serious according to the definitions given in section 7.1.

7.2.2 Causality

The PI must assess the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

7.2.3 Expectedness

The Chief Investigator (CI)/PI must assess the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

7.2.4 Severity

The CI/PI must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

7.3 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants’ medical notes (where appropriate) and the CRF.

7.4 Notification and reporting of Serious Adverse Events/ Sudden Unexpected Serious Adverse Reaction

All SAEs will be recorded in the participant medical notes, the CRF, the Sponsor SAE form and reported to the Sponsor (Joint Research Management Office) within 24 hours of the PI or co-investigators becoming aware of the event. Nominated co-investigators will be authorised

to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites.

All SUSARs that occur during the trial will be reported to the Sponsor within 24 hours of the PI or co-investigator becoming aware of the event. SUSARs should be reported to the Sponsor within 24 hours as the Sponsor has a legal obligation to report this to the Medicines and Healthcare products Regulatory Agency (MHRA) within 7 days (for fatal or life-threatening SUSARs) or 15 days for all other SUSARs. In the case of multicentre studies, the PI or the co-investigators at the participating site must inform the CI within 24 hours of the event. The CI or co-investigators at the co-ordinating site must inform the Sponsor immediately to allow reporting to the MHRA within the allocated timelines.

The original and any subsequent follow up of SAE forms, together with the fax confirmation sheet (if applicable) must be kept with the trial master file (TMF) at the study site.

7.5 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of trial participants from any immediate threat to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the Sponsor, Research Ethics Committee (REC) (via telephone) and the MHRA (via telephone for discussion with the medical assessor at the clinical trials unit) of this event **immediately**.

The CI has an obligation to inform both the MHRA and REC in writing within 3 days, in the form of a substantial amendment as per Sponsor standard operating procedures.

7.6 Annual safety reporting

The Development Safety Update Report (DSUR) will be sent by the CI to the Sponsor, the Research Ethics Committee (REC) and MHRA. The CI will carry out a risk/benefit analysis of the IMPs encompassing all events having arisen on the trial. The DSUR will be sent on the anniversary of the “notice of acceptance letter” from the MHRA. A copy of the DSUR and any associated correspondence with the MHRA will also be sent to participating sites.

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the REC "favourable opinion" letter from the REC) and to the Sponsor.

7.7 Overview of the safety reporting process

The CI has the overall pharmacovigilance oversight responsibility. The CI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the Sponsor's requirements.

8 REFERENCE SAFETY INFORMATION

Captopril- The reference safety information for this study for the ACE-I group will be Section 4.8 of the Captopril 50 mg tablets.

Losartan- The reference safety information for this study for the ARB group will be Section 4.8 of the Losartan Potassium 50 mg tablets (45.8mg of Losartan).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis

All analyses will be conducted according to intention-to-treat principles, meaning that all patients with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. The primary outcome will be analysed using a mixed-effect logistic regression model, with a random intercept for the minimisation variable trial centre. The model will be adjusted for minimisation variables planned surgical procedure (surgery involving the gut or all other surgery) and ACE-I/ARB category (ACE-I or ARB). The model will also be adjusted for the following pre-specified baseline covariates: age and gender (M/F). All covariates will be entered into the model as fixed factors. Age will be included as a continuous variable, assuming a linear association with the outcome. The magnitude of the treatment will be reported as an adjusted odds ratio with a 95% confidence interval. Significance will be set at $p<0.05$. Baseline demographic and clinical data for the two groups will be summarised but not subjected to statistical testing. A full statistical analysis plan will be developed and published online (https://www.qmul.ac.uk/ccpmg/) prior to analysis. Clinical outcomes are defined in appendix 2.

9.2 Sample Size

The primary outcome is myocardial injury defined according to high sensitivity plasma troponin measurement, within the first 48 hours after surgery. The incidence of postoperative myocardial injury in previous trials was ~40.0% in similar patients undergoing major surgery. An absolute decrease in the number of patients with troponin >99th centile of 20% (from 50% in the 'cessation' group to 30% in the 'continuation' group), with a built-in loss to follow up rate of 5% after surgery, would require a total sample size of **260 patients** (130 per group). This sample size will allow us to detect a 20% absolute risk reduction in the primary outcome measure, with a power of 90% and an overall type I error rate of 5%. Sample size calculations were performed using STATA 13.1 (StataCorp, College Station, TX). This will be conducted on an intention-to-treat basis i.e. all patients randomised during the study period will be included, and considered exposed to the intervention according to randomisation regardless of when the intervention was actually implemented.

10 DATA HANDLING & RECORD KEEPING

10.1 Confidentiality

The CI has a responsibility to ensure that patient confidentiality is protected and maintained. They must also ensure that participant identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and REC Approval.

The PI as well as the study team must adhere to these parameters to ensure that the patient's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, each patient, at time of consent must be allocated an unique screening number by either the PI or a member of the study team before undergoing any screening procedures. The patients initials (the first letter of their first name and the first letter of their last name) should be used as a means of pseudo-anonymising parameters. This information should be kept on a screening log, which should be updated accordingly throughout the study. Once the patient has completed screening procedures and is enrolled onto the study, the patient will be allocated a randomisation number.

No identifiable information will be collected from the subjects. The CI is the 'Custodian' of the data, and maintains access to the data. No patient identifiable details will be transferred outside the EU. Subjects maintain their right to revoke their authorisation for the use of their PID. The patients will be anonymised with regards to any future publications relating to this study.

10.2 Case Report Form

On data collection times illustrated in section 5.6, research study nurse will be responsible for the completion of the paper and electronic CRF throughout the life cycle of the study. The electronic CRF will be hosted on a secure, custom-designed trial Queen Mary University of London bespoke clinical trial database.

10.3 Record retention and archiving

At the end of the trial, as defined by GCP all documentation should be stored by each individual site's archiving facility, for a minimum of 20 years or the maximum period required by the Institution in which the trial will be conducted, whichever is longer. The Sponsor should be contacted prior to destruction.

A 'close out' visit will be conducted where all trial documentation will be prepared for archiving by that site. Records will be retained at each individual site. All records relating to the trial should be stored together, including the Investigator Site File (ISF), Pharmacy Site File (PSF) and CRF. It is the responsibility of the PI to ensure a full set of records is collated and documented.

In addition, source documentation (medical notes, images, results etc.) should be retained, as per local policy, for the duration of the archiving period.

10.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Policy Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, and all subsequent amendments, Trust and sponsor policies and procedures and any subsequent amendments.

In addition, sponsor auditors and Competent Authority inspectors will be allowed access to CRFs, source documents and other trial files to evaluate the trial. Audit reports will be kept confidential.

10.5 Ethical considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRMO to obtain Declaration of Sponsorships and approval.

10.6 Data management

A paper CRF will be used to collect data at site level. Data will be transcribed on to the paper CRF prior to entry on to the secure SPACE trial data web entry portal by the local site team.

10.7 Quality control and quality assurance

10.7.1 Summary monitoring plan

Monitoring will involve a review of the ISF as well as 10% of source data verification. This will involve direct access to patient notes at the participating hospital sites, which will include the review of consent forms and other relevant investigational reports. Missing data will be sought, unless confirmed as not available.

All sites will undergo an on-site site initiation visit. On site or remote monitoring visits will then occur within one month of the first patient being enrolled at a site and subsequently every six months or 10 patients whichever is sooner as per monitoring plan. At the end of the trial all sites will undergo an on-site or remote close out visit.

Non-commercial central facilities will be monitored during their participating in the trial, as detailed in the monitoring plan.

Refer to the study Monitoring Plan for full detail Monitoring will involve a review of the ISF as well as a proportion of SDV.

A summary of all monitoring activity for this study will be provided to the Sponsor at least every three or six months.

10.7.2 Audit and Inspection

This study may be audited by representatives from the coordinating centre and the Sponsor or its delegate. The investigator and institution will be informed of the audit outcome. Investigators are obliged to cooperate in any audit allowing the auditor direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor to discuss any findings or issues. An audit may occur at any time during or after completion of the study.

Inspections may be carried out by the Competent Authority at any time and the investigator should notify the Sponsor immediately if there are any such plans for an inspection.

10.8 Serious Breaches in GCP or the Trial Protocol

The Sponsor of the Clinical Trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial; or
- The protocol relating to the trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a 'serious breach', is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trials; or
- The scientific value of the trial.

The CI is responsible for reporting any serious breaches to the Sponsor (JRMO) **within 24 hours**. The Sponsor will notify and report to the MHRA within 7 working days of becoming aware of the serious breach.

11 TRIAL MANAGEMENT COMMITTEE

Day-to-day trial management will be co-ordinated by a trial management group consisting of the Chief Investigator and his/her support staff.

12 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be convened and chaired by and clinician independent to the study team and sponsor. Other members of the committee will be the CI, all PIs and at least 6 suitably qualified members. At least 3 of these will be independent.

Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- approving the final trial protocol
- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial
- reviewing relevant information from other sources
- considering recommendations from the DMEC and
- informing and advising on all aspects of the trial

13 DATA MONITORING AND ETHICS COMMITTEE

The Data Monitoring and Ethics Committee (DMEC) is independent of the trial team and comprises of a minimum of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. The principle responsibility of the DMEC will be to safeguard the interests of trial participants, including assessing the safety of the intervention, reviewing relevant new external evidence, and monitoring the overall conduct of the trial. The DMEC will provide recommendations about stopping, modifying or continuing the trial to the TSC. The DMEC may also make recommendations regarding selection, recruitment, or retention of participants, their management, protocol adherence and retention of participants, and procedures for data management and quality control. The TSC will be responsible for promptly reviewing the DMEC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required. The DMEC will review trial data relating to patient safety and the quality of trial conduct. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.

14 STUDY FINANCES

14.1 Funding sources

The study is British Oxygen Company research chair award in Anaesthesia, administered by the National Institute for Academic Anaesthesia.

14.2 Patient expenses/ payment

There are no participant study payments or travel expenses available for this study.

15 SPONSORSHIP AND INDEMNITY

Dr. Gareth Ackland of Queen Mary University of London the CI. Queen Mary University of London is also sponsoring the study.

16 PUBLICATION POLICY

This is an investigator-led study sponsored by the CI's substantive employer, Queen Mary University of London. The data collected will not be used to license/register any pharmaceuticals. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the design, TSC, accrual of eligible patients and statistical analysis. Contributing centres (and participating investigators) will be acknowledged in the final manuscript.

No participant may present data from his/her centre separately from the rest of the study results unless approved by the TSC and the sponsor.

17 REFERENCES

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6 Chae YK, Khemasuwan D, Dimou A, et al. Inhibition of renin angiotensin axis may be associated with reduced risk of developing venous thromboembolism in patients with atherosclerotic disease. *PLoS One* 2014;**9**:e87813

7 Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. *EMBO Mol Med* 2010;**2**:247-57

18 APPENDICES

Appendix 1: Duration of preoperative cessation required for SPACE trial.

Drug	Time required to stop drug preop (days)
Candesartan	2
Lisinopril	1
Irbesartan	2
Enalapril Maleate	1
Telmisartan	2
Ramipril	1
Eprosartan	2
Captopril	1
Losartan	1
Cilazopril	1
Olmesartan	2
Fosinopril Sodium	1
Valsartan	2
Moexipril Hydrochloride	1
Azilsartan	2
Perindopril	1
Quinapril	1
Trandolapril	5
Imidapril Hydrochloride	1

Appendix 2: Perioperative morbidity definitions for SPACE trial.

Respiratory events

Nosocomial pneumonia

Care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia. Nosocomial pneumonia will be characterized as early or late onset i.e. before or after first 4 days of hospitalization. Where repeated episodes of nosocomial pneumonia are suspected, a combination of new signs and symptoms and radiographic evidence or other diagnostic testing will be required to distinguish a new episode from a previous one. This category includes ventilator- associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or endotracheal tube), however care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia.

Nosocomial pneumonia must meet the following criteria:

Two or more serial chest radiographs with at least one of the following:

i) New or progressive and persistent infiltrate

ii) Consolidation

iii) Cavitation

And at least one of the following:

i) Fever (>38°C) with no other recognized cause

ii) Leucopaenia (<4, 000 WBC mm3) or leucocytosis (>12, 000 WBC mm3)

iii) For adults >70 years old, altered mental status with no other recognized cause

And at least two of the following:

i) New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements

ii) New onset or worsening cough, or dyspnoea, or tachypnoea

iii) Rales or bronchial breath sounds

iv) Worsening gas exchange

v) Need for invasive or non-invasive mechanical ventilation

Cardiovascular events

Hypotension: systolic blood pressure <90mHg either intraoperatively, or postoperatively within 72h of surgery.

Hypertension: Systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 100 mmHg.

Myocardial ischaemia or infarction: Acute ECG changes with appropriate clinical findings and changes in cardiac troponins ordered by attending clinicians.

Arrhythmia: ECG evidence of rhythm disturbance resulting in a fall in mean arterial pressure of greater than 20% and considered by clinical staff to be severe enough to require treatment (anti-arrhythmic agents, vasoactive agents, intra venous fluid, etc).

Cardiac or respiratory arrest: Clinical criteria according to UK Resuscitation Council Guidelines.

Acute heart failure: Appropriate clinical history and examination with consistent chest radiograph.

Acute kidney injury

A >26ϒμmol.L^{-1} increase in serum creatinine or sustained oliguria of <0.5 ml.kg^{-1} $hour^{-1}$ for twelve hours (KDIGO grade 1 or above).

KDIGO staging criteria

KDIGO Staging:

Staging	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥ 0.3mg/dl (≥26.5μmol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Infective complications

Infection, source uncertain

Two more of the following associated with strong clinical suspicion of infection (sufficient to require intra-venous antibiotic therapy):

i) Core temperature <36^{o}C or >38^{o}C

ii) White cell count >12 x 109 l-1 or <4 x 109 l-1

iii) Respiratory rate >20 breaths per minute or PaCO2 < 4.5 kPa

iv) Pulse rate >90 bpm

v) Radiological investigation for suspected sepsis

vi) Specimen/ blood samples sent for microbiological culture.

Urinary tract infection

A symptomatic urinary tract infection must meet at least one of the following criteria:

i) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38oC), urgency, frequency, dysuria, or suprapubic tenderness and patient has a positive urine culture, that is, >105 microorganisms per cm3 of urine with no more than two species of microorganisms.

ii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38^{o}C), urgency, frequency, dysuria, or supra- pubic tenderness and at least one of the following:

a. positive dipstick for leucocyte esterase and/or nitrate;
b. pyuria (urine specimen with >10 WBC mm-3);
c. organisms seen on Gram stain of unspun urine;
d. at least two urine cultures with repeated isolation of the same uropathogen with >102 colonies/ mL in non-voided specimens;
e. >105 colonies/mL of a single uropathogen in a patient being treated with an effective antimicrobial agent for a urinary tract infection;
f. physician diagnosis of a urinary tract infection;
g. physician institutes appropriate therapy for a urinary tract infection.

Other infections of the urinary tract (kidney, ureter, bladder, urethra, etc.)

Other infections of the urinary tract must meet at least one of the following criteria:

i) Patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site.

ii) Patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation or during a histopathologic examination.

iii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38^{o}C), localized pain, or localized tenderness at the involved site and at least one of the following:

iv) Purulent drainage from affected site;

v) Organisms cultured from blood that are compatible with suspected site of infection

vi) Radiographic evidence of infection, for example, abnormal ultrasound, computed tomography or magnetic resonance imaging;

vii) Physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space;

viii) Physician institutes appropriate therapy for an infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space.

Surgical site infection SSI (superficial incisional)

A superficial SSI must meet the following criteria:

i) Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following:

a. purulent drainage from the superficial incision.

b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.

c. at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.

d. diagnosis of superficial incisional SSI by the surgeon or attending physician.

Surgical site infection (deep incisional)

A deep incisional SSI must meet the following criteria:

i) infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following.

ii) Purulent drainage from the deep incision but not from the organ/ space component of the surgical site.

iii) A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38^{o}C) or localized pain or tenderness, unless incision is culture-negative.

iv) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
v) Diagnosis of a deep incisional SSI by a surgeon or attending physician. An infection that involves both superficial and deep incision sites should be classified as a deep incisional SSI.

Surgical site infection (organ/space)
An organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers that is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection. Listed later are the specific sites that must be used to differentiate organ/space SSI. An example is appendectomy with subsequent sub-diaphragmatic abscess, which would be reported as an organ/space SSI at the intra-abdominal specific site. An organ/space SSI must meet the following criteria:
Infection occurs within 30 days after the operative procedure if no implant is left in
place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and patient has at least one of the following:
i) Purulent drainage from a drain that is placed through a stab wound into the organ/space.
ii) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space.
iii) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
iv) Diagnosis of an organ/space SSI by a surgeon or attending physician.

Laboratory - confirmed bloodstream infection
Laboratory - confirmed bloodstream infection must meet at least one of the following
criteria:
i) Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.
ii) Patient has a fever (>38oC), chills, or hypotension and at least one of the following:
   a. common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.
   b. common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.
   c. positive antigen test on blood. And signs and symptoms and positive laboratory results are not related to an infection at another site.

Other defined postoperative complications

Postoperative haemorrhage

Overt blood loss requiring transfusion of two or more units of blood in two hours.

Gastrointestinal bleed

Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz, in practice from the oesophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel and colon.

Other postoperative haemorrhage (not gastrointestinal bleed)

Blood loss within 72 hours after the start of surgery, which would normally result in transfusion of blood.

Stroke

Clinical diagnosis with confirmation by CT scan.

Limb or digital ischaemia

Sustained loss of arterial pulse (as determined by palpation or Doppler) or obvious gangrene.

Multi-organ dysfunction syndrome

A life threatening but potentially reversible physiologic derangement involving failure of two or more organ systems not involved in the primary underlying disease process.

Acute psychosis or delirium

Acute episode of severe confusion or personality change, which may result in hallucinations or delusional beliefs in the absence of a pre-existing diagnosis, which may account for the clinical symptoms and signs.

Pulmonary embolism

Computed tomography (CT) pulmonary angiogram with appropriate clinical history.

Acute respiratory distress syndrome

According to consensus criteria:

i) Suitable precipitating condition (many causes exist).

ii) Acute onset diffuse bilateral pulmonary infiltrates on chest radiograph.

iii) No evidence of cardiac failure or fluid overload (PAOP < 18 mmHg);

iv) Either: PaO_2:FiO2 < 40 kPa = Acute Lung Injury

PaO_2:FiO_2 < 27 kPa = Acute Respiratory Distress Syndrome.

Gastro-intestinal bleed

Unambiguous clinical evidence or endoscopy showing blood in gastro-intestinal tract.

Bowel infarction

Demonstrated at laparotomy.

Anastamotic leak

Demonstrated at laparotomy or by contrast enhanced radiograph or CT scan.

Perforated viscus

Clinical diagnosis demonstrated at laparotomy or confirmed by contrast enhanced radiograph or CT scan. For example perforated bowel, gall bladder etc.

Paralytic ileus

Persistent clinical evidence of intestinal ileus and failure to tolerate enteral fluid or feed associated with valid cause.